Inflammation and Atherosclerosis

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Atherosclerosis

A pathological process that causes:

- Coronary artery disease
  - Angina pectoris
  - Myocardial infarction
- Cerebrovascular disease
  - Ischemic stroke
  - Vascular dementia
- Peripheral vascular disease
  - Gangrene

Risk factors:

High plasma cholesterol

High blood pressure

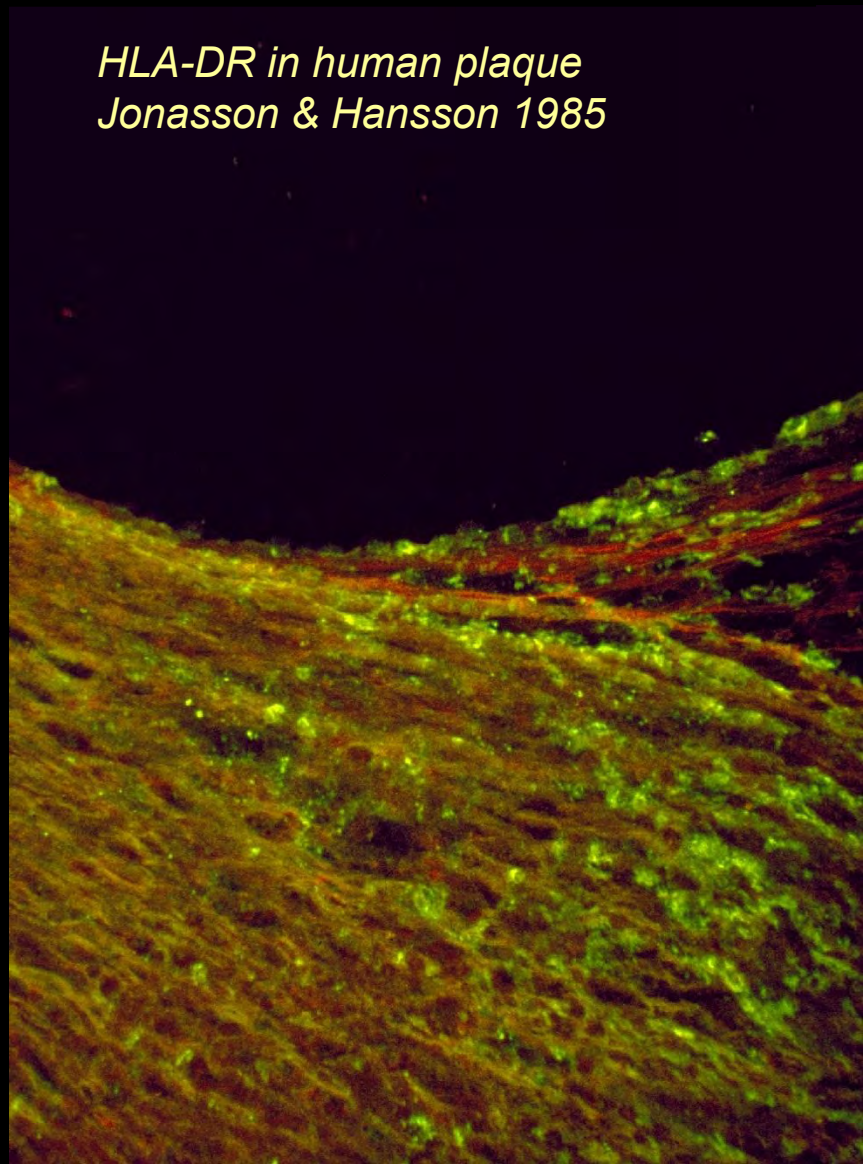
Smoking

Diabetes

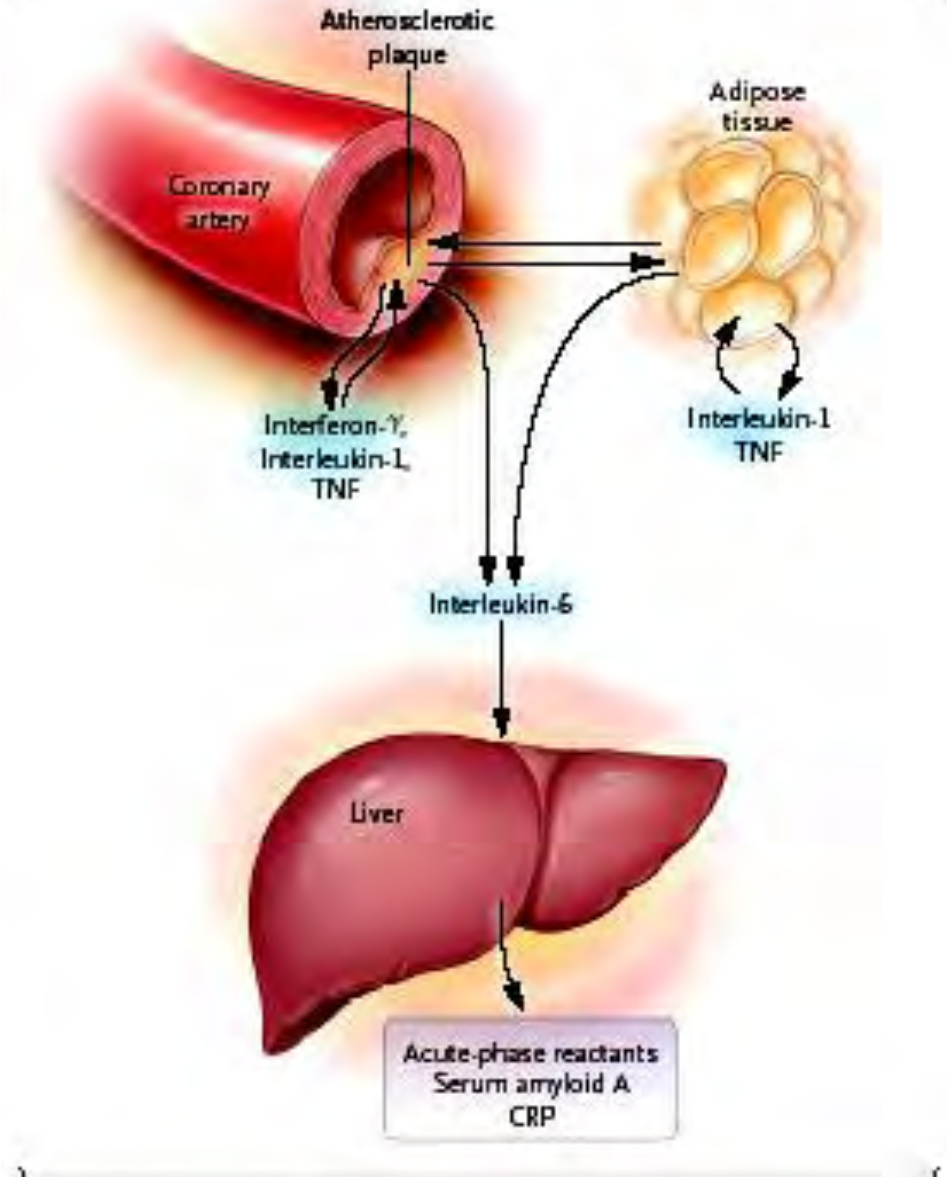
Inflammation

Atherosclerosis is an inflammatory disease

- **Immune activity in plaque**
  - T cells, Macrophages
  - HLA, costimulatory factors, and cytokines
- **Systemic response**
  - CRP, IL-6, Antibodies
- **Genetic association**
  - Alleles of immune and inflammatory genes
- **Immunopathogenesis**
  - Major effects of immune factors in model organisms



Inflammation in coronary arteries leads to release of inflammatory mediators into circulation - and triggers acute phase reaction in liver



GK Hansson
N Engl J Med 2005; 352:1685-95

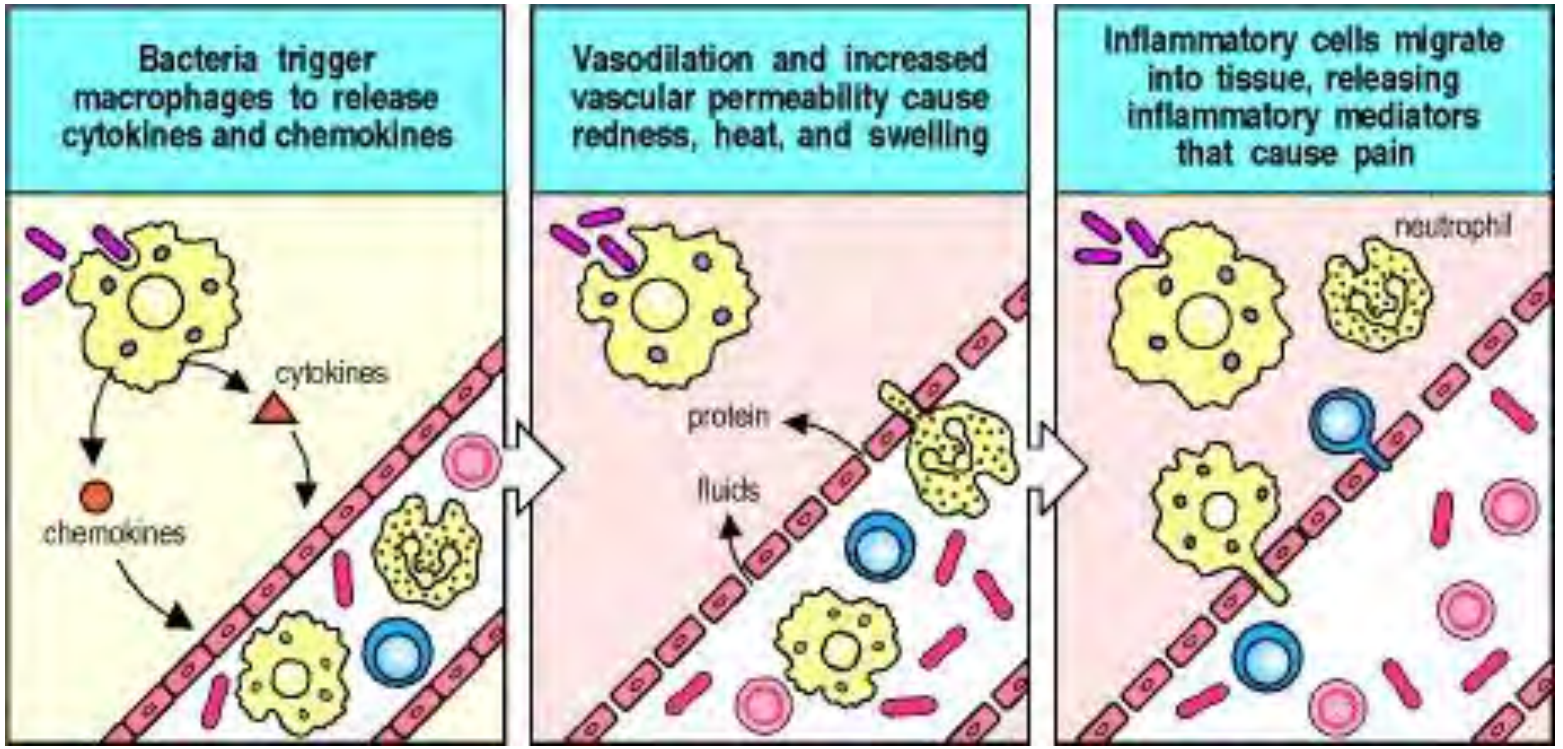
Inflammation (Latin, *inflammare*, to set on fire) is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.

Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process.

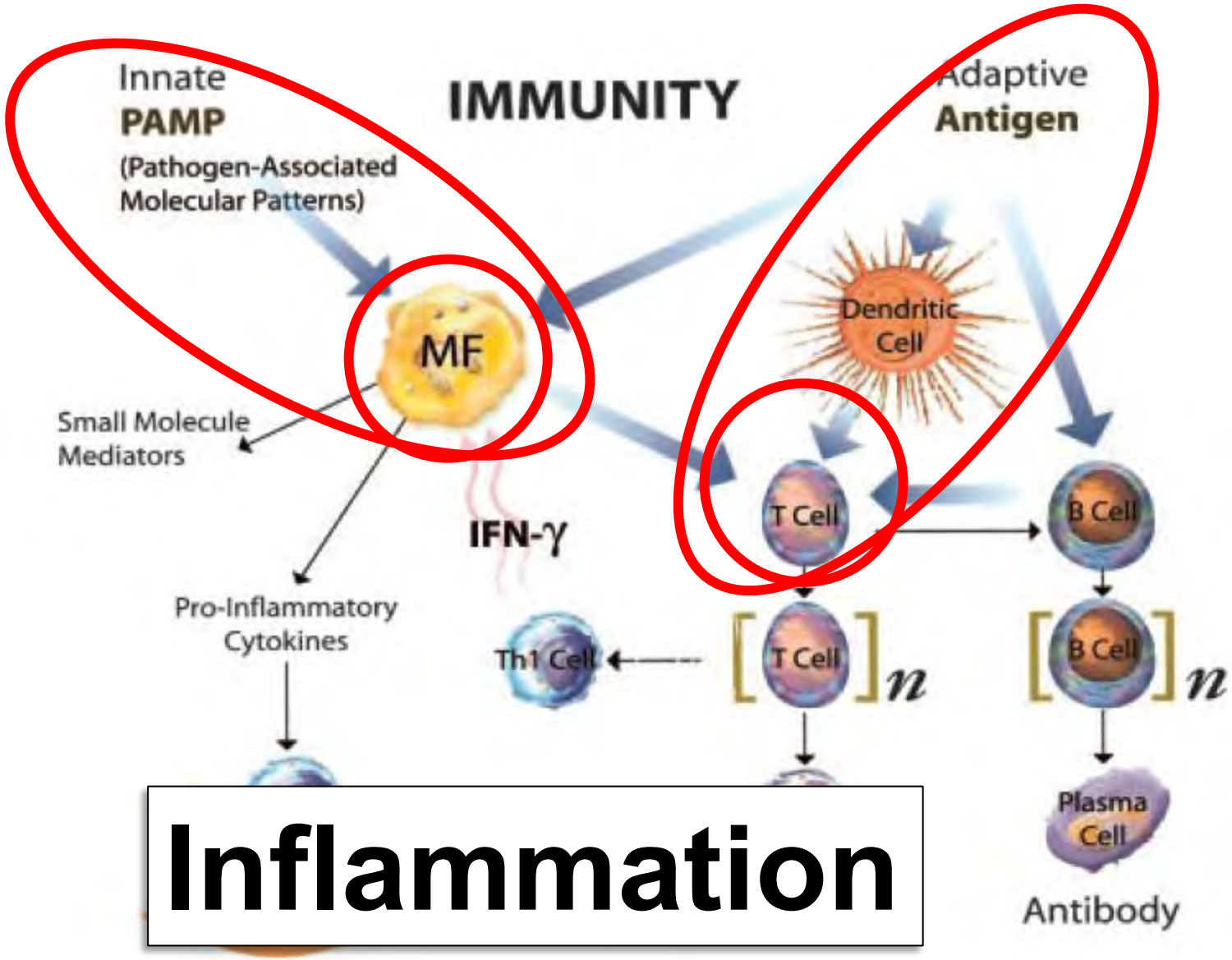
A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue.

Wikipedia

Inflammation is typically triggered when bacterial pathogens invade the organism

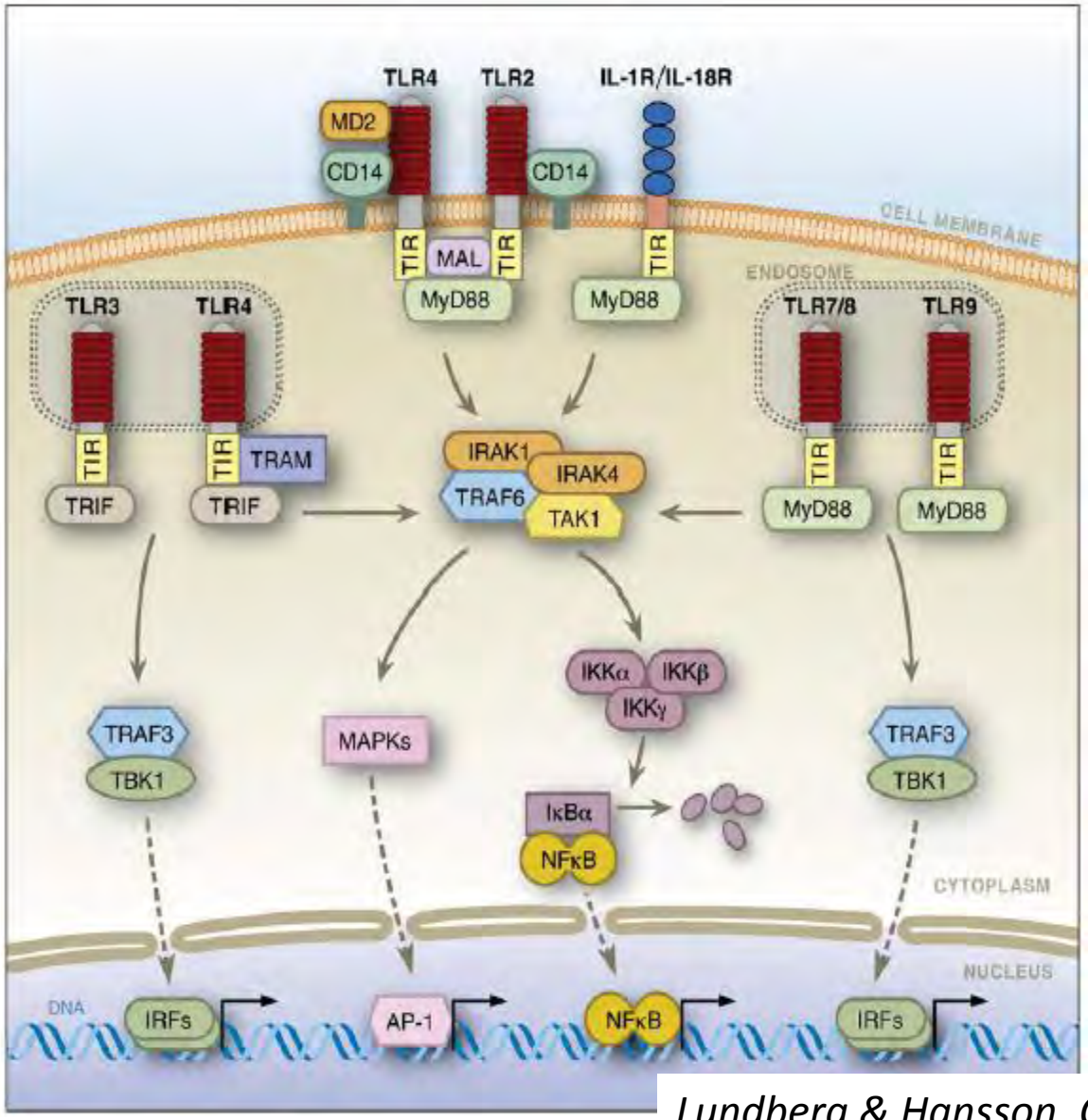


Janeway´s Immunobiology, 5th Ed.



Hansson-Libby-Schönbeck-Yan, Circ Res 2002

Toll-like receptors recognizing pathogen molecules trigger inflammation



Lundberg & Hansson, Clin Immunol 2010

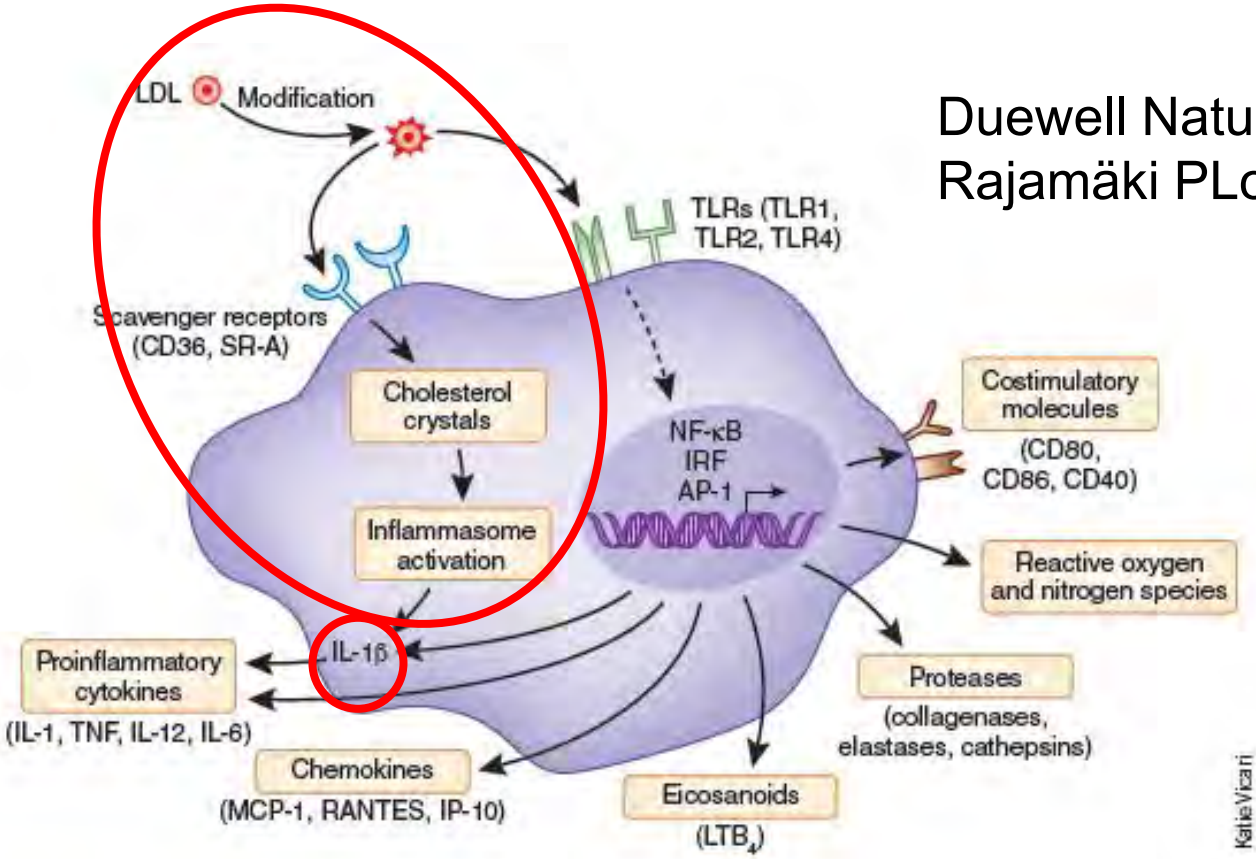
Toll-like receptors can also recognize danger-associated endogenous molecules

Table 1 Endogenous TLR ligands associated with inflammation.

Ligand	Function	TLR
Hsp60	Stress inducible cytosolic heat shock protein	TLR2/TLR4
Hsp70	Stress inducible cytosolic heat shock protein	TLR2/TLR4
Gp96	Stress inducible ER heat shock protein	TLR2/TLR4
HMGB1	Chromosomal binding protein	TLR2/TLR4
ApoCIII	Apolipoprotein in VLDL	TLR2
mRNA	Intracellular nucleic acid	TLR3
Fibrinogen	Acute-phase protein	TLR4
Fibronectin EDA	ECM component	TLR4
Heparan sulfate	ECM component	TLR4
Hyaluronan fragment	ECM component	TLR4
β-defensin 2	Cationic antimicrobial peptide	TLR4
Oxidised phospholipid	Component of oxLDL	TLR4
mmLDL	Lipoprotein modified by mild oxidation	TLR4
Nucleic acids	RNA/DNA-containing immune complex	TLR7/TLR9

Lundberg & Hansson, Clin Immunol 2010

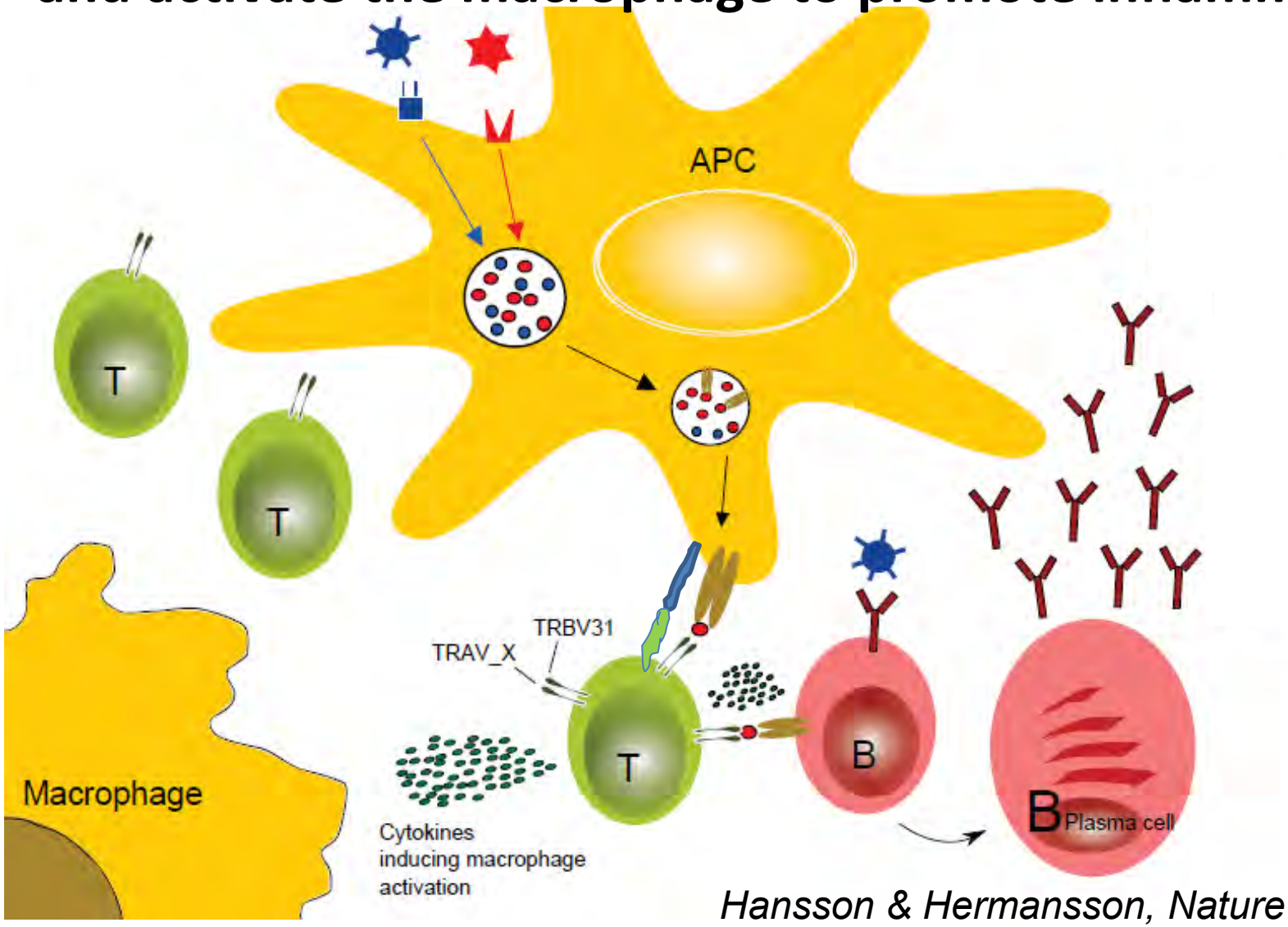
Innate immune response of macrophages is initiated by cholesterol crystals that activate the inflammasome



Duewell Nature 2010
Rajamäki PLoS One 2010

Hansson & Hermansson, Nature Immunol 2011

The activated T cell can instruct the B cell to make antibodies to its cognate antigen, and activate the macrophage to promote inflammation



Hansson & Hermansson, Nature Imm 2011

Two types of immunity

Innate

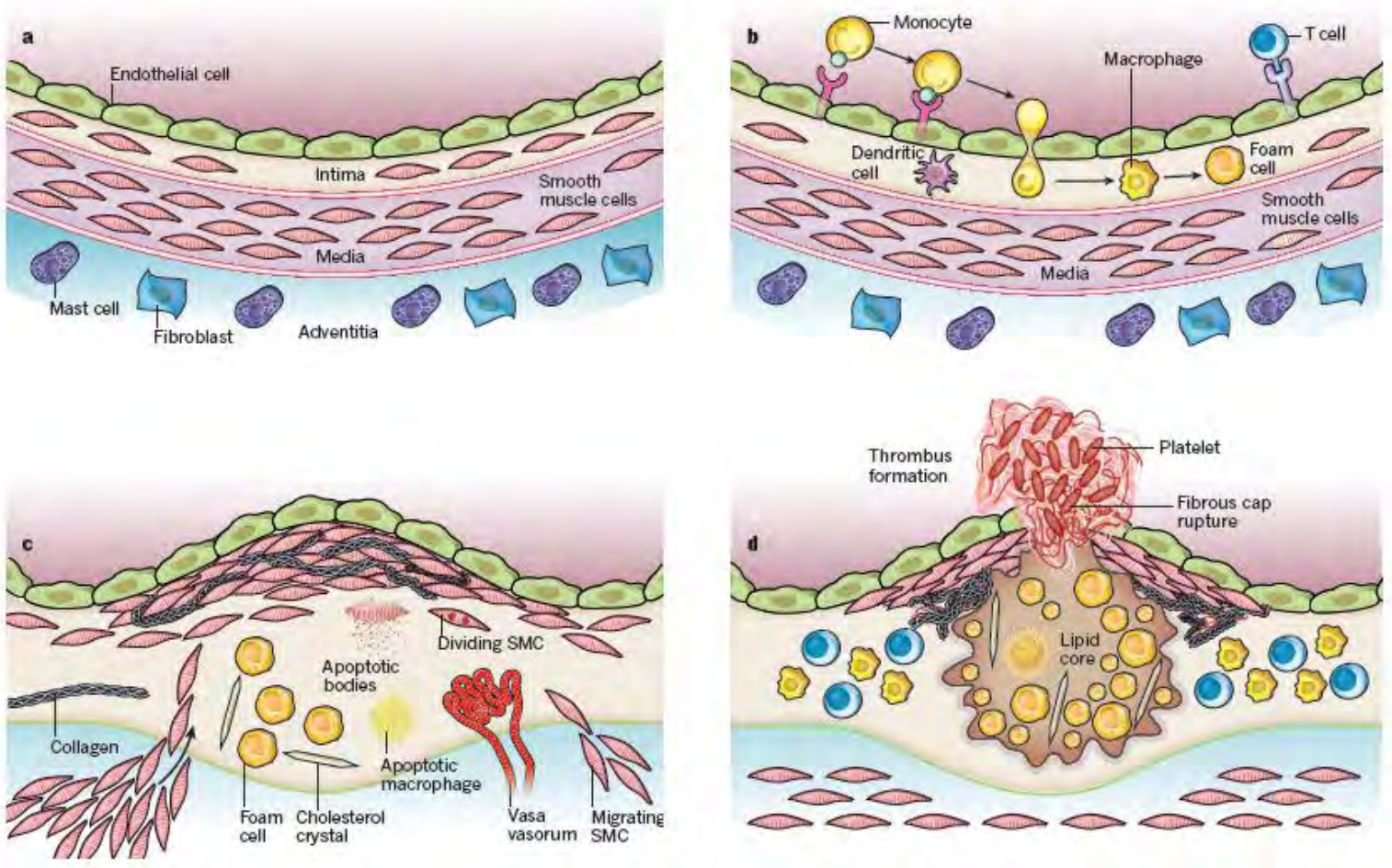
- Macrophages, EC and other cells
- Receptors are germ-line encoded
- Broad specificities
- Modest affinities
- Rapid
- Stupid (= no memory)

Adaptive

- T and B cells
- Receptors generated by somatic rearrangement
- MHC restriction
- High specificity and affinity
- Slow
- Clever - memory

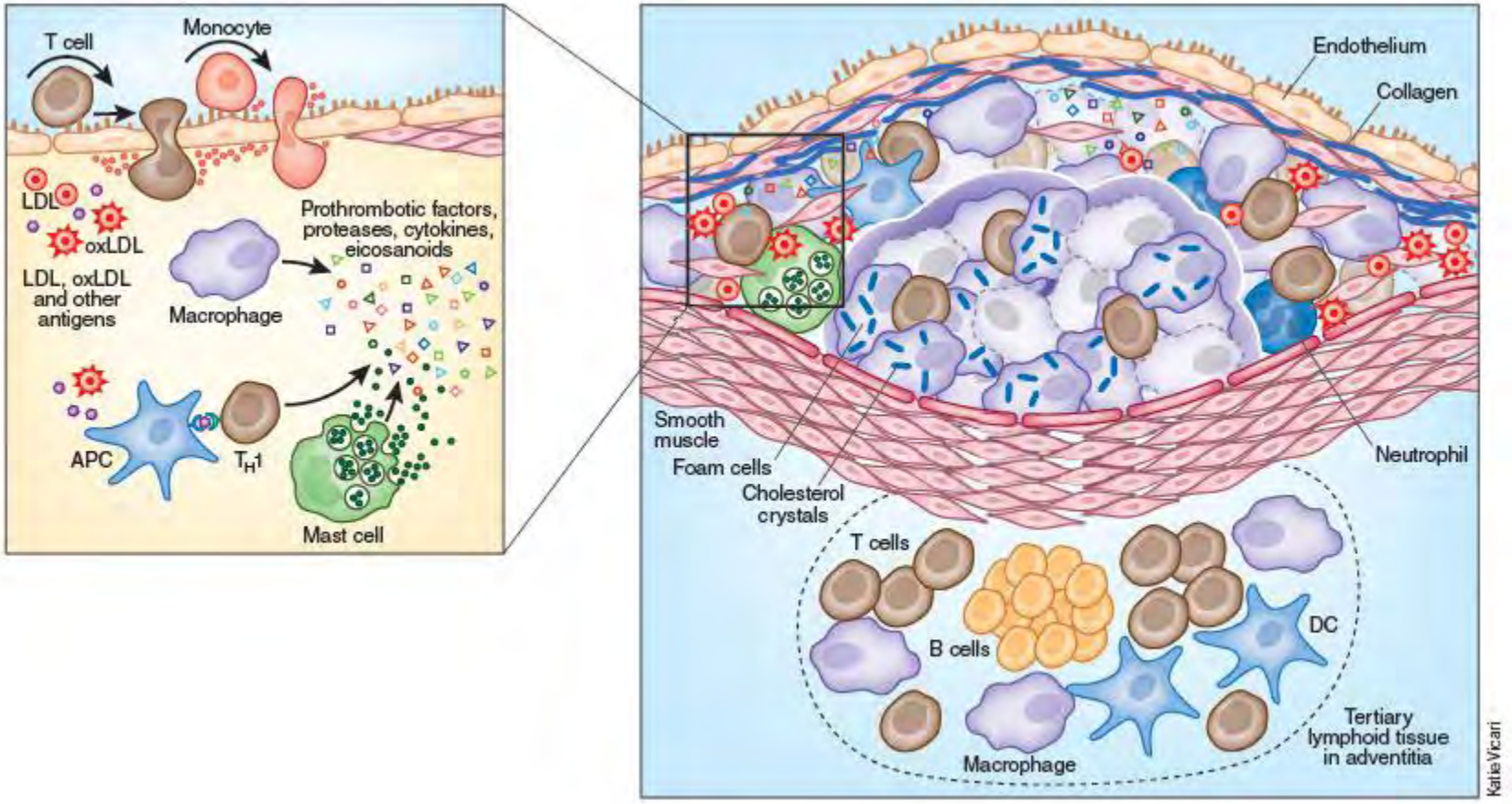
Macrophages and T cells accumulate at sites of LDL retention in the forming atherosclerotic plaque

INSIGHT REVIEW



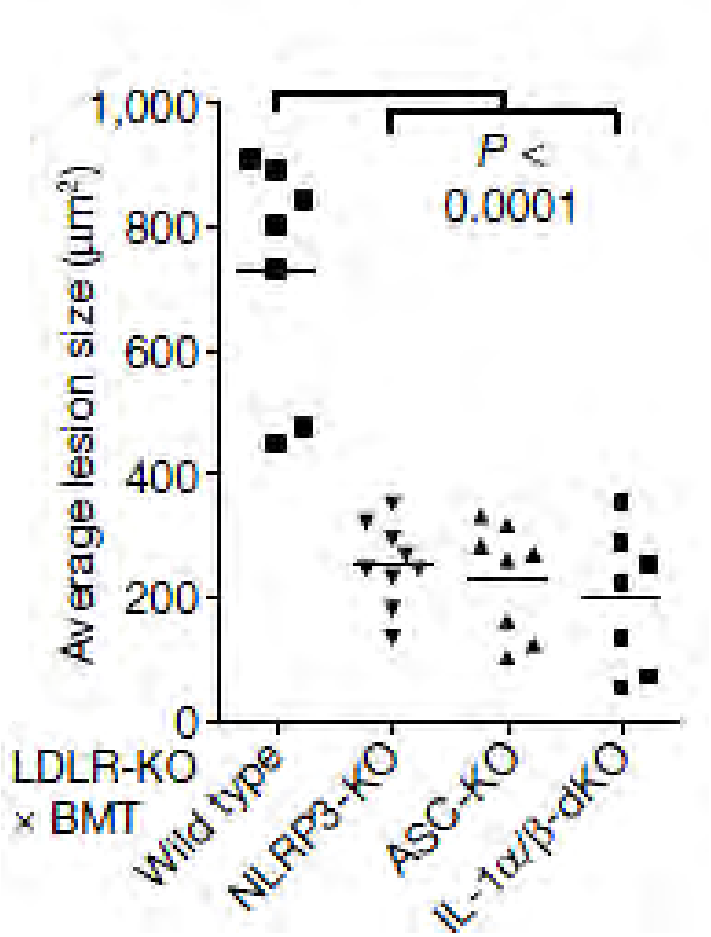
Libby, Ridker & Hansson, Nature 2011

The atherosclerotic plaque – a site of immune inflammation



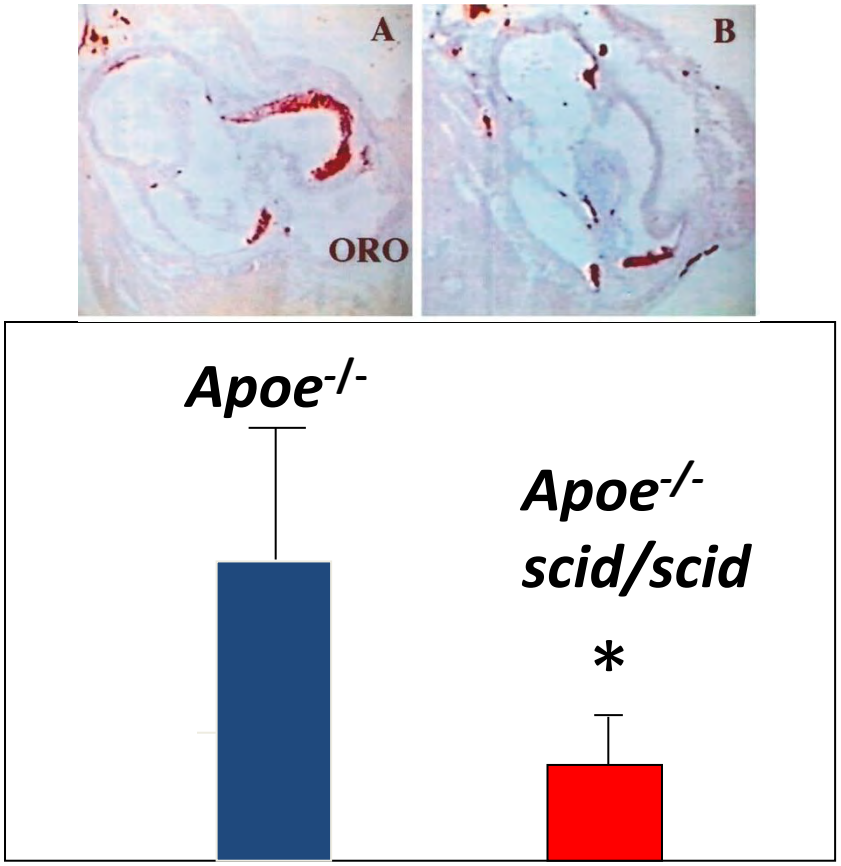
Hansson & Hermansson
Nature Immunol 2011

Lack of IL-1β or NLRP3 inflammasome of innate immunity dramatically reduces atherosclerosis



Duewell et al, Nature 2010

Lack of adaptive immunity leads to dramatic reduction in atherosclerosis



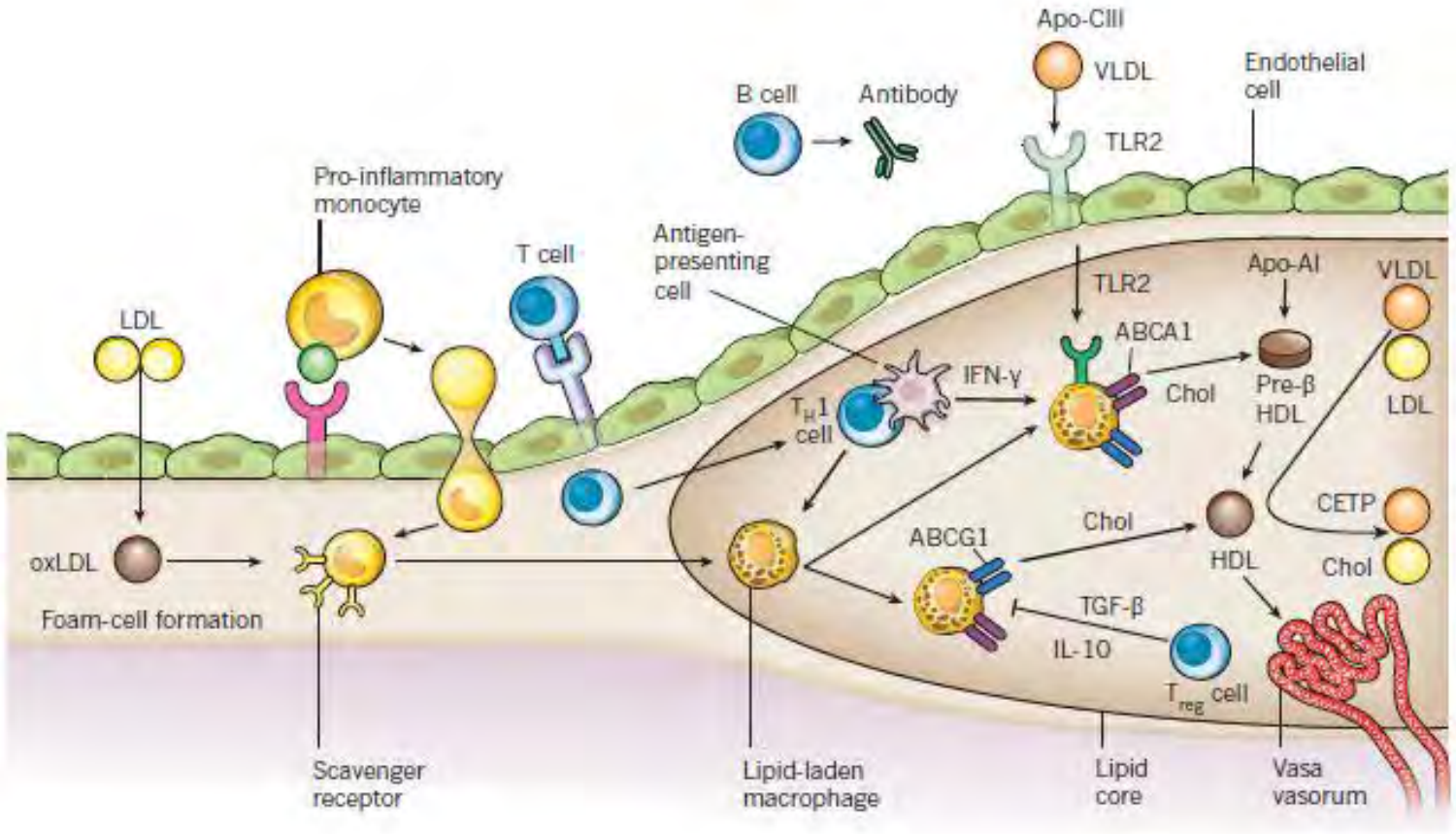
Zhou et al, Circ 2000

INFLAMMATION, ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE

State-of-the-art for atherosclerosis

- The disease process is an inflammation triggered by LDL accumulation
- Inflammation is an independent risk factor
- Current markers (hsCRP) are informative – their use in screening debated
- Antiinflammatory therapies should be evaluated for effects on CVD
    - TNF blockers / RA; methotrexate; statins

Innate and adaptive immune reactions cause progression of atherosclerosis



Libby, Ridker & Hansson, Nature, May 19, 2011

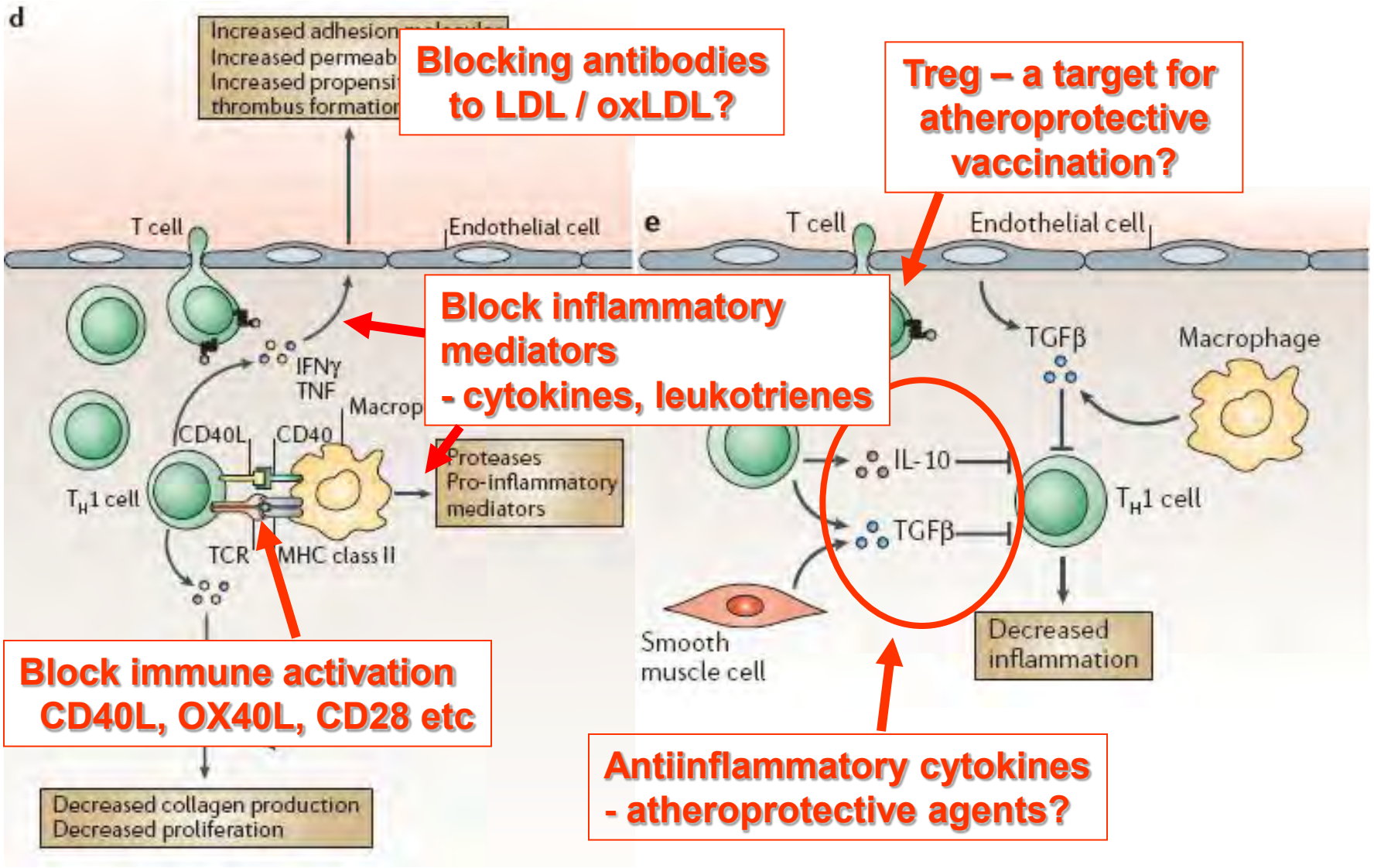
Mediators of cardiovascular inflammation

- **Proinflammatory immune cytokines**
  - IL-1β, IL-18, TNF, Lymphotoxin, Interferon-γ
- **Cell surface molecules of immune cells**
  - CD40-CD40L; CD137-CD137L; OX40L-OX40; LIGHT-LTβR
- **Eicosanoids**
  - Prostaglandins
  - Leukotrienes

Vascular effects of cytokines

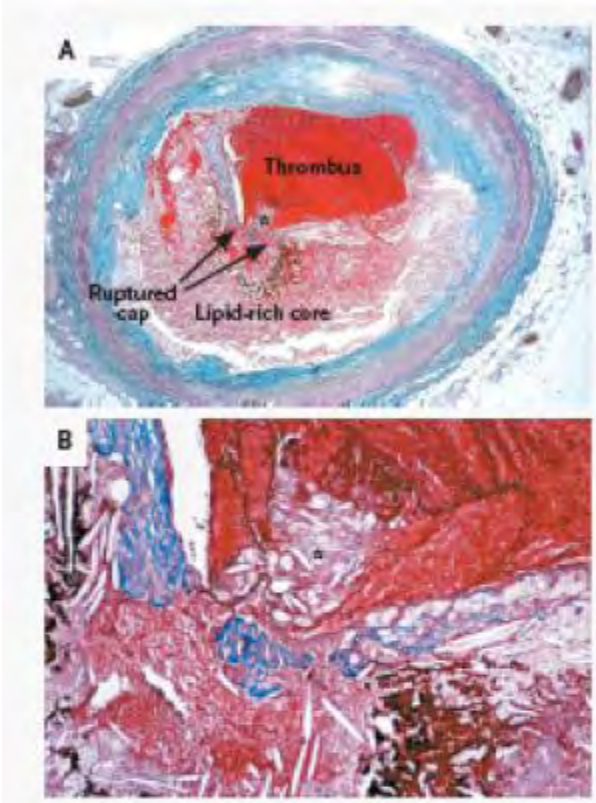
- Interferon-γ
  - Activate EC / MHC, LAM
  - Inhibit SMC prolif, α-actin; collagen
  - Promote MMPs, iNOS
- TNF superfamily
  - Activate EC / LAM, permeability
  - Promote MMPs, NOS
  - Cytotox (esp w IFN-γ)
  - Regulate lipid metabolism (TNF - LPL, LIGHT - HL)
  - Regulate mineralization (RANKL)

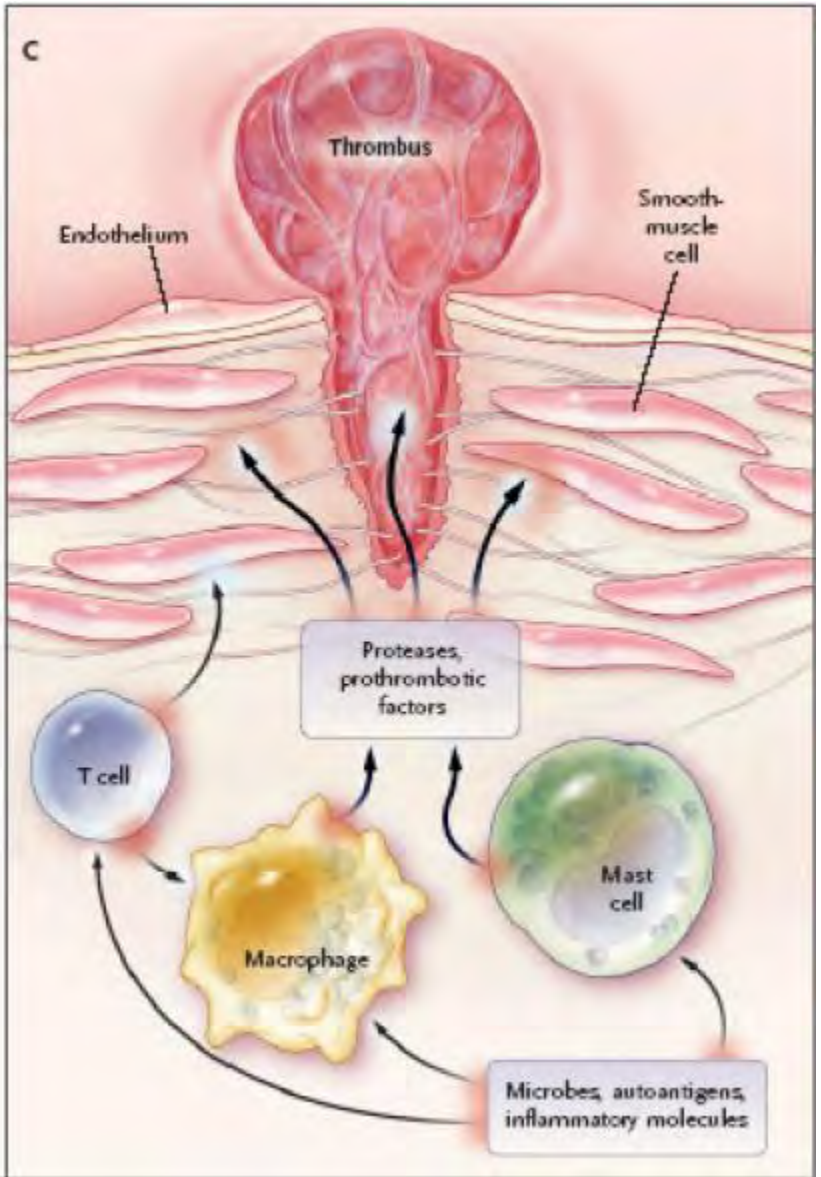
Therapeutic opportunities



GK Hansson & P Libby, Nature Rev Immunol 2006; 6:508-519

Plaque rupture and thrombosis





Micrographs: E Falk

GK Hansson
N Engl JMed 2005

Challenges in translating the biology of atherosclerosis to the clinic

- Animal models have provided detailed information about pathogenesis and novel principles for therapy
- But animal models, although needed, are not perfect mimicks of human disease
- Animal models are well suited for studying initiation and progression of atherosclerosis
- But we lack models for plaque activation and atherothrombosis

Challenges in translating the biology of atherosclerosis to the clinic

- Genomics has provided therapy targets and validation but limited fundamental novel information
- Atherosclerosis seems to depend on gene-environment interactions with a large number of genes, each of which makes a small contribution

Progress in translating the biology of atherosclerosis to the clinic

- Humanize mouse models
  - Lipoproteins, HLA etc
- Model plaque activation, rupture, thrombosis
- Develop better biomarkers
  - Proximal immune mediators; plaque components
- Use imaging to monitor human disease
  - High-resolution anatomic; molecular imaging
- Biobank patients
  - DNA; Patological tissue: mRNA-protein-metabolites
- Clinical trials as a laboratory for discovery
- *P Libby, PM Ridker, GK Hansson, Nature , May 19, 2011*

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